Crystal structure of β2-adrenergic receptor as a new template in homology modeling of GPCR. Application to serotonin 5-HT7 receptor

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Introduction

The 5-HT_7 receptor is the latest identified serotonin (5-hydroxytryptamine, 5-HT) receptor subtype. The brain distribution of 5-HT_7 receptors suggests their significant role in many mental diseases[1].

Until Oct. 2007 the best template for homology modeling of this (and others) serotonin receptor was bovine rhodopsin. The recent publication of X-ray structure of β2-adrenergic receptor delivers another template, which seems more appropriate for modeling serotonin, and other biogenic amine receptors, as their evolutionary distance to β2R is closer than to the rhodopsin.

We have examined the use of β2R template in modeling of 5-HT_7R and the prediction of binding modes of known high affinity antagonists. New models predict similar ligand positions within the binding pocket, however some differences are also visible.

Methodology

The population of several hundreds models were produced using MODELER software, based on the alignment considering most conserved residues in the GPCR family. Ligands were built in 3D using web-based CORINA, optimized in Sybyl and docked in Flexx with constraints. Docking was followed by consensus scoring in Sybyl, using 4 additional scoring functions. Showed solutions have top PMF scores and were ranked 5 in consensus scoring.

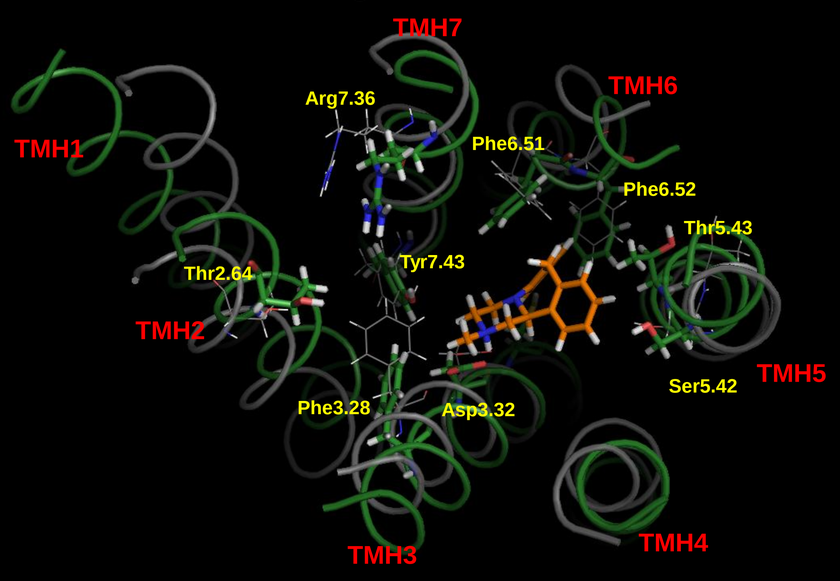

Fig. 1: The alignment of rhodopsin-based (grey) and β2-based models (green). Mianserin is docked to β2-based model.

Acknowledgement

This study was partly supported by the Network "Synthesis, structure and therapeutic properties of compounds and organic substances" coordinated by the Institute of Organic Chemistry Polish Academy of Sciences.

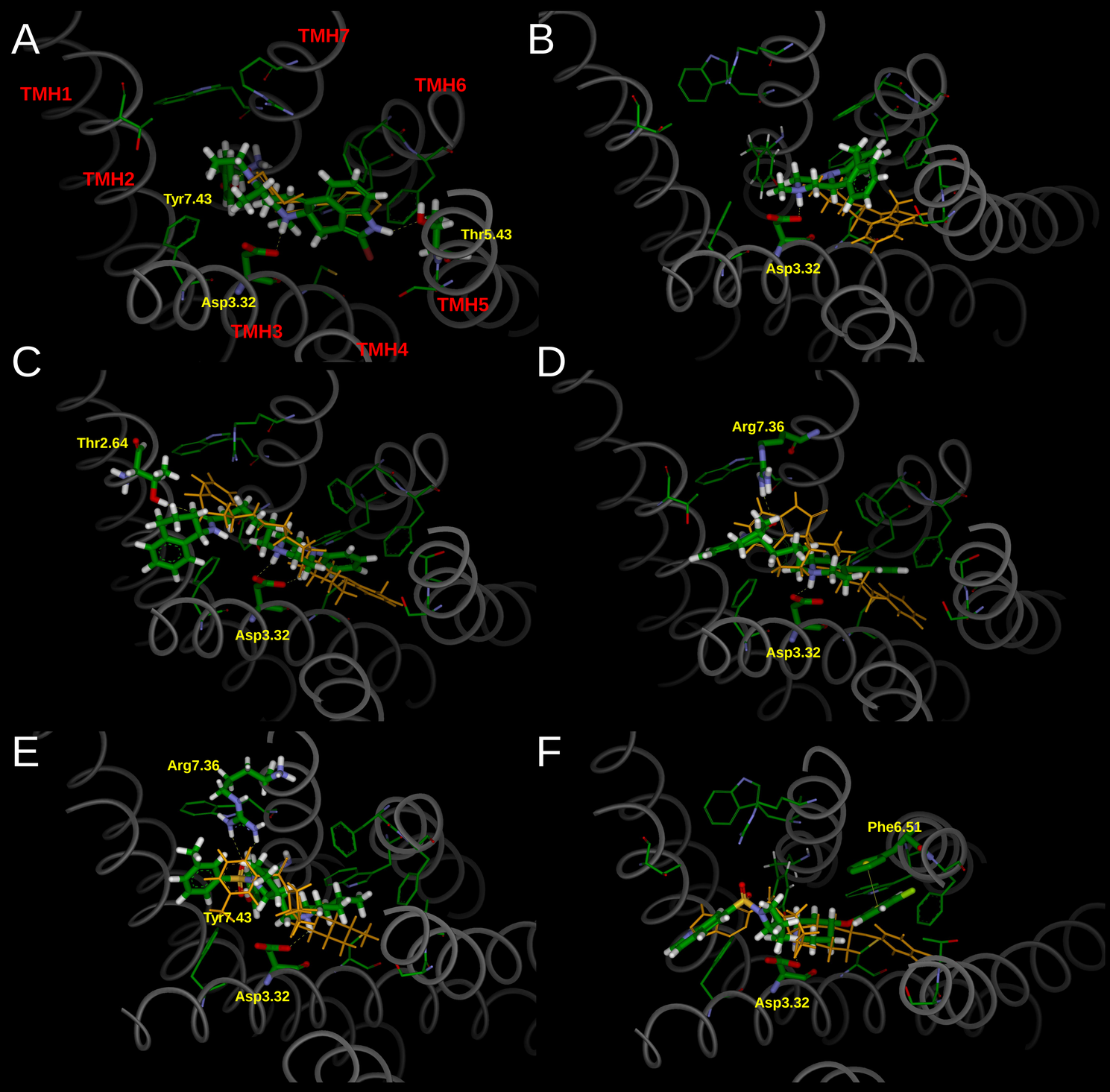

Fig. 2: Representative 5-HT_7 antagonists docked to β2-based models of 5-HT_7R. Docked ligands are repersented as sticks and compared to „old" binding poses obtained using rhodopsin based models (line representation colored orange). Aminoacids that formed specific interactions are shown as sticks. Examples represent the following groups of ligands (after [2]): A - ergolines, B – tricyclic antipsychotics, C – arylpiperazines, D – arylpiperidines, E,F – sulfonamides.

Results

The complexes obtained using new models, compared to the previously published rhodopsin based models [2], show similar binding orientations of docked ligands. Aromatic moieties of ligands are placed within the binding cavity formed by TMHs 3-6. Basic amine groups always form ionic bond with Asp3.32.

Similarities:

The binding modes of all the classes of 5-HT_7 antagonists are maintained in the new models.

Differences

[i]: the shape of the binding cavity is different. Phe6.52, that in rhodopsin-based models formed CH-π edge-to-face interactions with ligand aromatic rings, is less exposed in new models (close vicinity of Cys3.36, that constitutes a steric hindrance for the ligand). No ligand was able to penetrate the binding pocket deep enough of form specific, low-energy contact with Phe6.52.

[ii]: linear-shaped ligands (like long chain arylpiperazines) show more horizontal orientation within the pocket compared to rhodopsin based models.

Conclusion

Models based on β2-adrenergic receptor template do not offer the straightforward improvement as a serotoninergic ligand modelling tool. The usability of new models as targets for massive virtual screening have to be additionally evaluated in the separate experiment.

References

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[2] Kołaczkowski M. et al. J. Med. Chem. (2006) 49, 6732-6741